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Real-World Evidence — What Is It and What Can It Tell Us?

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Real World Data

- Refers to information on health care that is derived **from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing data, product and disease registries, and data gathered through personal devices and health application**

Key to understanding the usefulness of real

- Key to understanding the usefulness of real-world evidence is an appreciation of **its potential for complementing t**he **knowledge** gained from **clinical trials (whose well-know limitation make it difficult to generalize findings to larger, more inclusive population of patients**, providers, and health care delivery systems or setting that reflect actual use in practice

- A real-world evidence can inform therapeutic development, outcomes research, patient care, research on health care system, quality improvement, safety surveillance, and well-controlled effectiveness.

- Real-world evidence can also provide information on how factors such as clinical setting and provider and health-system characteristics influence treatment effects and outcomes.

- Saving time and money while yielding answers relevant to broader populations of patients than would be possible in a specialized research environment.

Two key dimensions of real-world evidence

1. The setting in which the evidence is generated, which includes the population defined by the data source, and the specific methods used to collect and curate the data on that population.

2. The methodologic approach used to conduct the surveillance or research.

Research settings- traditional trials vs real-world

- “Traditional” clinical trials are often conducted with specific populations and in specialized environments that differ from the realities of clinical or home settings.

- Measures design to control variability and to ensure the quality of the data they generate, such as the eligibility criteria, detailed case-report forms (separate from ordinary medical records, and intensive monitoring and specialized research personnel to ensure adherence to protocol, and precision in data collection

- Clinical trial unquestionably remains a powerful tool for developing scientific evidence about the safety and efficacy of a medical product while informing our understanding of the biologic mechanisms involved in its therapeutic action.

- Trials are needed to provide an essential element of premarket evaluation of medical product- **namely, robust evidence that a treatment may "work"**

- However, **the internal validity attained in these trials is often achieved at the expense of uncertainty about generalizability**, since population enrolled may differ in significant ways form those seen in practice.

- There may be few data on interactions with concomitant illness and treatment, and adherence may be supported by intensive efforts that are infeasible in practice.

- **GROWING EXPENSE OF TRIALS**

Data sources raises concerns

- EHR and claim data are not collected, organized with the goal of supporting/optimizing research, and the accuracy and reliability of data gathered by personal devices and health-related apps are unknown.

- Social media data sources raises questions about the quality of the data, and privacy issue.

- NIH, FDA, etc.. Working on harmonizing the data

- **Development of large-scale distributed research networks and computable phenotypes (i.e., conditions or patients characteristics that can be derived from EHRs** and claims data without requiring external review or interpretation that allow researchers to identify cohorts of interest across multiple data source.

Research methods, treatment allocation, and the definition of real-world evidence

- Real-world evidence can be used across a wide spectrum of research, ranging from observational studies to studies that incorporate planned interventions, with or without randomization at the point of care.

- It is **incorrect to contrast the term "real-world evidence" with the use of randomization** in a manner that implies that they are **disparate or even incompatible concepts.**

- Adapting the tools and methods of traditional trials to real-world settings—**considering component to obtain valid results and minimizing bias.**
- Planned intervention (RCT or non-RCT) can be used in both the tertiary care and academic environments.

RCTs conducting in a real-world setting

- Salk Polio
- ADAPTABLE
- There is an extensive literature on pragmatic RCTs designed to inform decision making at the individual and population level.
- **Cluster randomization**, useful for evaluating interventions at the level of health system, practices or hospitals.

- Real-world evidence **is valuable in observational settings**, for use of generating hypothesis for prospective trials, assess the generalizability of findings from interventional trials (RCTs), examine changes in patterns of therapeutic use, and measure and implement quality in health care delivery.

- Hope??Access to real world data when **paired with development of more robust method will allow greater use of observational treatment comparisons** in **drawing causal inferences about treatment effects of medical products.**

- Although observational studies are an essential tool for clinical epidemiologic investigations, quality improvement, and safety surveillance, **their finding require judicious evaluation when used to assess treatment effects**.

- These limitation are particularly problematic when an observational study is used to evaluate the effectiveness of a medical product and the **expected or observed effect is relatively small.**

- It can be difficult to be confident that **the effect is not due largely or wholly to confounding factors.**

Conclusions

- The term “real-world evidence” is used, **the primary attribute that distinguishes it other kind of evidence is related to the context in which the evidence is gathered.**

- **clinical care and home or community settings as opposed to research-intensive or academic environment**. The **distinction should not be based on the presence or absence of a planned intervention or the use of randomization.**

- **Real-world research** and the concepts of a **planned intervention and randomization** are entirely **compatible**

Conclusions

- **One of the most important advances in clinical trial methodology may be the broadening of the application of randomization outside more typical venues for clinical trials**, such as academic centers.

- In order to gain collective confidence in the appropriate uses of this array of methods across disparate settings, we must first be clear about our terminology and its application.

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The Magic of Randomization versus the Myth of Real-World Evidence

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Box 1. Facilitation of Randomization to Enhance Patient Care and Protect Public Health.

Randomization Provides Evidence about Treatment Effects That Can Be Trusted

Randomization results in groups of patients that are balanced (give or take the play of chance) with respect to their risks of all types of health outcomes. Consequently, in sufficiently large randomized trials, the effects of a treatment can be reliably assessed.

Nonrandomized observational studies may be able to detect large treatment effects. However, the potential biases can be appreciable, so such studies cannot be trusted when the benefits or harms of a treatment are actually null or only moderate.

Obstacles to Randomized Trials Should be Removed to Protect Patients

Increased focus on adherence to rules rather than on the scientific principles that underlie randomized trials has substantially increased the complexity and cost of trials.

Promotion of nonrandomized analyses of databases as a rapid source of "real-world evidence" about the effects of treatments is a false solution to the problems caused by the bureaucratic burdens imposed on randomized trials.

Instead, obstacles to randomized trials should be removed to allow more new treatments to become available and to facilitate the reliable assessment of existing treatments.

Box 2. Opportunities to Improve the Quality and Efficiency of Randomized Trials of New and Existing Interventions.

Appropriate trial guidelines

Based on scientific principles: Focus on issues that can materially affect the reliability of the results (including randomization with concealed assignment, adherence to trial intervention, completeness of follow-up, and intention-to-treat analyses).

Developed in partnership: Create new guidelines that can be adapted for many different types of trials through a collaboration of regulators, investigators, patients, and funders.

Enhanced recruitment

Faster and more predictable: Access electronic health care record systems and specialized registries to identify large numbers of potentially eligible patients.

Broader and more generalizable: Avoid unduly restrictive inclusion and exclusion criteria so that the results are relevant to a wide range of patients.

Improved quality

Better adherence: Implement interactive electronic case-report forms to help ensure complete and consistent data collection and to enhance adherence to the protocol and safety procedures.

Centralized monitoring: Improve patient safety and trial performance through real-time monitoring and analysis of electronic data from local trial sites.

Effective follow-up

Complete and comprehensive: Minimize loss to follow-up and facilitate prolonged follow-up of health outcomes by linkage to electronic health record systems.

Extended range of outcomes: Enhance the assessment of the safety and efficacy of treatment by incorporating technological advances (e.g., smartphones and digital sensors).